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An Analytical Study on Global Pharmacovigilance Regulations and their Role in Risk Management

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ABSTRACT

This analytical study examines how global pharmacovigilance (PV) regulations operationalize risk management across the product lifecycle and proposes practical tools and a convergence roadmap for regulators and Marketing Authorization Holders (MAHs). Context & Rationale. Post-marketing risks evolve as exposure broadens, indications expand, and real-world heterogeneity reveals safety issues not seen in trials. Since the thalidomide crisis, PV has been shaped by ICH E2 guidelines, EU GVP, and large safety databases (VigiBase, EudraVigilance, FAERS). Harmonization has delivered interoperability (E2B[R3]), common terminology (MedDRA), and lifecycle integration, yet meaningful divergence persists in governance (QPPV/PSMF), expedited reporting clocks, signal methods, and risk-minimization frameworks (US REMS vs EU RMP). Problem. Despite common references (ICH, MedDRA), MAHs face variable expectations across expedited reporting, periodic reports (DSUR/PBRER), PASS, RMMs, device vigilance, and emerging areas (RWE, AI, patient-generated data), creating duplication, cost, and uncertainty. Objectives & Methods. The study (i) compares PV/device frameworks across EU, US, UK, Japan, Canada, India; (ii) maps how regulations operationalize risk management (RMP/REMS, PASS, governance); (iii) develops a 12-domain capability maturity model and heatmap; (iv) builds transferable tools (DSUR↔PBRER crosswalk, model RMP checklist, compliance scorecards, SDEA outline); (v) analyzes five case studies; and (vi) derives a 12–24 month convergence roadmap. Methods blend doctrinal analysis, structured maturity scoring, and case-based synthesis with defined scoring criteria and inter-rater checks.

Keywords: VigiBase, Eudra Vigilance, FAERS, ICH, MedDRA

INTRODUCTION

Background and Rationale

Medicines and vaccines deliver profound public health benefits, yet residual risks persist even after regulatory approval. These risks evolve post-marketing as:

- Patient exposure increases (larger, more diverse populations),
- Indications expand (new therapeutic areas), and
- Real-world heterogeneity reveals novel safety issues not detected in clinical trials.

Pharmacovigilance (PV) is the scientific and regulatory discipline that systematically identifies, evaluates, and mitigates these risks. Since the thalidomide crisis of the 1960s, PV has matured through successive waves of regulatory reform and global harmonization:

- ICH E2 Guidelines standardized reporting and risk management approaches.
- EU GVP Modules formalized Good Pharmacovigilance Practices as binding obligations.
- Global safety databases such as VigiBase, EudraVigilance, and FAERS enabled large-scale international signal detection.

Achievements of Harmonization

- Interoperability: E2B(R3) standards for Individual Case Safety Reports (ICSRs).
- Consistency: Universal adoption of MedDRA terminology for coding adverse events.
- Lifecycle integration: Risk management is now seen as a continuous obligation, not a one-time regulatory hurdle.

Persistent Fragmentation

Despite harmonization, jurisdictional divergence persists in:

- Governance: Requirement for Qualified Person for PV (QPPV) and Pharmacovigilance System Master File (PSMF) differs between EU and other regions.
- Reporting rules: Different clocks (e.g., 7-day vs 15-day ICSR deadlines) and thresholds for expedited reporting.
- Signal detection methodologies: Statistical algorithms vary across agencies.
- Risk minimization measures (RMMs): US REMS (Risk Evaluation and Mitigation Strategies) vs EU RMP (Risk Management Plans).

METHODOLOGY

Study Design

A mixed methods analytical study was employed, integrating:

- **Comparative legal/regulatory analysis** of statutory texts, GVP modules, and guidance documents.

- **Structured scoring** of jurisdictions across 12 PV capability domains.
- **Case-based evaluation** to contextualize regulatory decisions.

This design ensures triangulation of doctrinal, empirical, and case-driven evidence.

Table.1: Data Sources

Source Type	Agencies/References	Scope
Primary	ICH E2 series (E2A, E2B(R3), E2C(R2), E2D, E2D(R1) draft, E2F)	International harmonization standards
	EU GVP Modules I–XVI; EMA Eudra Vigilance (EV) & ADRreports portals	EU pharmacovigilance & transparency
	FDA REMS guidance; FAERS database	US regulatory safety management
	MHRA PV & UK-specific PSMF/QPPV framework	Post-Brexit UK system
	PMDA GVP/GPSP; Japanese RMP	Japan regulatory framework
	Health Canada RMP & Canada Vigilance Program	Canadian PV
	CDSCO/PvPI guidance	Indian PV landscape
	EU MDR/IVDR; MDCG Q&As	Device vigilance
Secondary	CIOMS WG VII/VIII reports	Consensus best practices
	Peer-reviewed analyses	Independent evaluation
	Official press releases	Regulatory updates

Table 2: PV Capability Scoring Criteria

Score	Criteria
0	Absent – no formal requirement
1	Fragmented – partial, limited scope
2	Basic – explicit but narrow provisions
3	Developing – standardized processes, limited IT support
4	Advanced – structured, integrated with oversight
5	Fully mature – digitized, transparent, audited, globally interoperable

Domains (12): Governance, ICSRs, Signals, Periodic Reports, PASS, RMM Design, RMM Effectiveness, Transparency, Inspections, Data/IT, Patient Engagement, Device Vigilance.

Inter-rater reliability: 15% sample double-coded; Cohen's κ ≥0.75 as benchmark.

Discrepancies resolved through consensus adjudication.

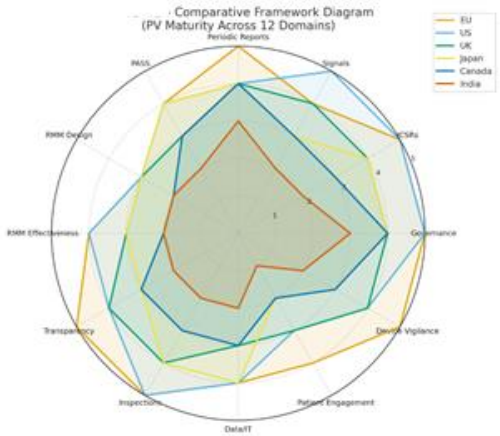

Figure 1: Comparative Framework Diagram

Signal Detection & Assessment Methods

- **Quantitative disproportionality analysis**: PRR, ROR, IC, EBGM from EV, FAERS, VigiBase.
- **Qualitative assessment**: clinical triage, literature surveillance, aggregated review of PBRER/PSUR/DSUR.
- **Escalation pathway**: structured decision rules for confirmation → label change → PASS initiation → RMM implementation.

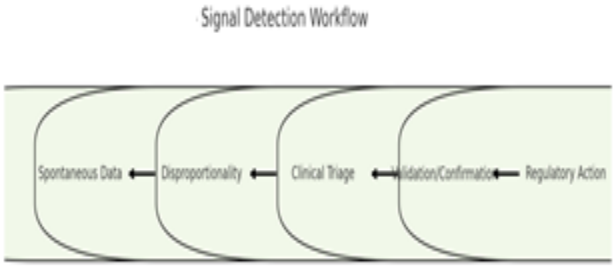

Figure 2: Signal Detection Workflow

Table 3: Case Selection and Analysis

Isotretinoin	Fetal risk	Risk–benefit balancing & REMS models
Clozapine	Agranulocytosis	Intensive blood monitoring
CAR T therapies	Cytokine release syndrome	Adaptive PV for ATMPs

Ethics and Quality

- Only **public/officially published data** were used.
- **No identifiable patient data** accessed.
- A **Quality Management Plan (QMP)** included:
  - Protocol version control.
  - Audit trails for coding.
  - Reproducible scorecard templates.

Data Synthesis

- **Heatmaps** constructed for jurisdictional maturity comparison.
- **Scorecards** developed for domain-by-domain analysis.
- **Narrative synthesis** aligned to the 12 domains.

Objectives of the Review

The primary objective of this comprehensive review is to critically discuss the role of Artificial Intelligence in transforming pharmacy education and its impact on pharmaceutical learning, clinical training, and research practices. The review aims to explore various AI technologies and their applications in pharmacy teaching, personalized learning systems, virtual simulations, clinical decision support, drug discovery, assessment methods, and research-oriented educational approaches [41]. Additionally, this review seeks to evaluate the major benefits associated with AI integration in pharmacy education, including enhanced student engagement, improved learning outcomes, competency-based education, and advanced clinical skill development. The review also highlights the challenges and limitations related to AI implementation, including ethical concerns, academic integrity issues, data privacy risks, algorithmic bias, financial constraints, and technological infrastructure limitations [42].

RESULTS AND DISCUSSION

Harmonization Heatmap

The comparative analysis across **six jurisdictions (**EU, US, UK, Japan, Canada, India) demonstrates both zones of strong convergence and areas of regulatory divergence. Twelve

pharmacovigilance (PV) domains (D1–D12) were scored on a maturity scale of **0–5**, with "5" representing digitized, transparent, and auditable systems**.**

- **European Union (EU)** emerges as the global benchmark, consistently scoring **5** across most domains. The EU has institutionalized QPPV/PSMF structures, electronic submissions (E2B R3), and integrated device vigilance (MDR/IVDR)**.** Its transparency portals and PASS requirements serve as global best practices.
- **United States (US)** follows closely, though REMS–RMP d**i**vergence and limited integration of device vigilance reduce comparability. Sentinel and RWE integration bolster maturity in signal detection and periodic reporting.
- United Kingdom (UK) remains aligned with the EU, but post-Brexit adaptations (UK-specific PSMF, QPPV) introduce nuances.
- Japan shows balanced progress, with mandatory RMPs and strong database PASS infrastructure, though its transparency practices are less developed.
- **Canada** demonstrates solid adoption of international standards but lags in RMM effectiveness measurement and data interoperability. The obligation for hospital ADR reporting is a unique strength.
- **India** shows steady progress under PvPI**,** but remains constrained by limited PASS design, data interoperability challenges, and weak device vigilance integration**.**

DSUR–PBRER Crosswalk

The comparative mapping of Development Safety Update Reports (DSURs) and Periodic Benefit–Risk Evaluation Reports (PBRERs) highlights their complementary but partially overlapping functions.

- **DSURs** emphasize cumulative trial safety data and protocol amendments**,** while PBRERs focus on real-world benefit–risk evaluation.
- Harmonization opportunities lie in aligning **safety** specifications, cumulative exposure tables, and ongoing/planned studies.
- A cross-referenced template could reduce duplication and facilitate smoother lifecycle integration.

Model RMP Checklist (Excerpt)

A model Risk Management Plan (RMP) checklist was constructed to operationalize monitoring using Key Risk Indicators (KRIs).

- The safety specification domain emphasizes the need for continuously updated epidemiology and real-world data.
- Pharmacovigilance plans (routine + targeted) are benchmarked against timelines and registry completeness.
- Risk minimization measures (RMMs)—both routine (labeling, SmPC, PIL) and additional (educational programs, pregnancy prevention, controlled distribution) are linked with measurable KRIs such as % prescribers trained, compliance with testing, and timeliness of label updates**.**

Case Studies (Condensed Summaries)

Five historical and contemporary case studies illustrate how regulatory pathways and PV mechanisms shape outcomes:

- **Valproate (EU/UK):** Despite strengthened pregnancy prevention programs, adherence gaps highlight the need for sustained patient engagement**.**
- **Isotretinoin (US iPLEDGE, EU):** Controlled access systems reduced teratogenic risk, but created equity and accessibility challenges**.**
- **Clozapine (EU, Japan):**
  Electronic lab monitoring frameworks ensured effective agranulocytosis control, yet compliance gaps persist.
- **Rofecoxib (US/EU):**
  Failure to escalate early cardiovascular signals underscored the importance of robust signal validation frameworks**.**
- **CAR T therapies (US):**
  Adaptive PV strategies, including REMS with ETASU, demonstrate the evolving governance needed for advanced therapies**.**

Table 4: PV Domain Maturity Scores by Jurisdiction

Domain	EU	US	UK	Japan	Canada	India	Notes
D1 Governance (QPPV/PSMF)	5	3	4	4	3	3	EU fully codified QPPV/PSMF; India emerging
D2 ICSRs (E2B[R3] standards & timelines)	5	4	4	4	4	3	EU leads with EV; India lagging
D3 Signal management framework (GVP IX-like)	5	4	4	4	3	3	CIOMS aligned; India partial
D4 Periodic reporting (PBRER/PSUR/DSUR)	5	4	4	4	4	3	All harmonized to ICH, India adapting
D5 PASS infrastructure/requirements	5	4	4	4	3	3	Weak PASS in LMICs
D6 RMM/REMS/RMP design	5	4	4	4	4	3	REMS vs RMP divergence
D7 RMM effectiveness evaluation	4	3	3	3	3	2	Global weakness in measuring impact
D8 Transparency/public dashboards	5	4	4	3	3	3	EU EV portal best practice
D9 Inspection/audit framework	5	4	4	4	3	3	Inspections mature in EU/US
D10 Data/IT interoperability	5	4	4	3	3	3	E2B R3 gaps outside EU/US
D11 Patient engagement/communication	4	4	4	3	3	3	Weak across most regions
D12 Device vigilance interface	5	3	4	3	3	2	EU MDR/IVDR integration

							strongest

Table 5: DSUR–PBRER Crosswalk

Domain	DSUR Section	PBRER Section	Interlock / Cross Reference
Serious risks	Section 15 – Significant Findings	Section 16 – Signal & Risk Evaluation	Cross-reference for alignment with RMP safety specification
Cumulative exposure	Section 7	Section 7.3.3	Harmonized stratification (age, sex, region, indication)
Ongoing/planned studies	Section 11	Section 16.3; RMP Part III	Ensures transparency of PASS/registries

Table 6: Model RMP Checklist with KRIs

RMP Component	Content	KRIs (Examples)
Safety specification	Important identified/potential risks; missing information; epidemiology; off-label use	% of safety concerns with updated epidemiology data
PV Plan	Routine (ICSRs, PSURs) + targeted (PASS, registries)	% PASS on schedule; registry data completeness
RMM – routine	Labeling, SmPC, PIL	% label updates within timelines
RMM – additional	Educational tools, controlled distribution, PPPs, lab monitoring	% prescribers trained; % certified pharmacies; lab compliance rates; pregnancy testing compliance

Table 7: Case Study Synopsis

Case	Jurisdiction(s)	Risk Focus	RMM Applied	Outcome / Lessons
Valproate	EU/UK	Teratogenicity	Pregnancy prevention program, label revisions	Reduced exposure but adherence gaps
Isotretinoin	US (iPLEDGE), EU	Teratogenicity	Controlled access, prescriber/pharmacy certification	Risk reduction but equity challenges
Clozapine	EU, Japan	Agranulocytosis	Lab monitoring with electronic verification	High effectiveness; adherence gaps persist
Rofecoxib	US/EU	Cardiovascular risk	Post-market withdrawal	Illustrates signal maturation necessity
CAR T therapies	US	Cytokine release syndrome	REMS with ETASU, evolving to labeling	Adaptive PV for novel therapies

Table 8: Jurisdictional PV Strengths & Weaknesses

Jurisdiction	Strengths	Weaknesses
EU	Codified governance (QPPV/PSMF); centralized EV; transparency dashboards	Heavy administrative burden; RMM evaluation uneven
US	Targeted REMS; pragmatic risk-based focus	Fragmented governance; less standardized signal framework
UK	Mirrors EU constructs; strong QPPV requirements	UK-specific addenda cause duplication
Japan	RMPs institutionalized; strong PASS and transparency	Less digitized IT backbone
Canada	Emphasis on addenda to global dossiers; pragmatic reporting	Limited PASS and IT interoperability
India	Rapidly evolving PvPI/CDSCO framework; guidance updates	RMM evaluation and device vigilance still weak

Table 9: Best Practice Implications

Principle	Implication	Illustration (KRI Example)
Proportionality	Reserve additional RMMs only for risks labeling cannot address	% high-risk products with additional RMMs
Close the loop	Mandate RMM evaluation with endpoints	% RMMs retired/modified after evaluation
Digital operating model	Automate reporting & signal dashboards	Median ICSR processing time
Transparency & patient centricity	Publish plain-language RMPs	% RMPs with patient summaries

Table 10: Convergence Roadmap

Milestone	Action	Timeframe
Standards alignment	Adopt ICH E2D(R1); harmonize DSUR & PBRER formats	Short-term (3 yrs)
Signal governance	Establish global minimum expectations	Short-term (3 yrs)
AI-assisted detection	Explainable AI with human validation	Mid-term (5 yrs)
RMM analytics	Common KRI library; visualization templates	Mid-term (5 yrs)
Capacity building	Vigi Flow onboarding, MedDRA training	Long-term (10 yrs)
Combination vigilance	Unified committees; PSUR/PSMF linkages	Long-term (10 yrs)

CONCLUSION

Global PV has strong harmonized pillars but remains fragmented at the points that matter for day-to-day execution reporting clocks, RMM triggers and evaluation, device interfaces, and acceptance of RWE/AI. The consequence is duplicated effort for MAHs, uneven inspection focus for regulators, and avoidable latency in identifying and mitigating patient risk.

What should change—practical takeaways:

1. **Unify lifecycle reporting:** Adopt a joint DSUR↔PBRER core template with shared exposure tables and signal sections to remove redundancy and tighten trial–post-market handoffs.

2. **Standardize RMM analytics:** Agree a minimal global metric pack (reach, adherence, outcome change) and retirement criteria for RMMs/REMS to close the effectiveness loop.
3. **Codify signal governance:** Define minimum expectations for detection →validation→action SLAs, with transparent audit trails across jurisdictions.
4. **Digitize the operating model:** Ensure clean E2B(R3)flows, automated timeliness/quality dashboards, interoperable data dictionaries to reduce manual reconciliations.
5. **Adopt explainable AI with guardrails:** Use ML for triage and temporal patterning under documented validation, human oversight, and auditability standards.
6. **Elevate patient centricity:** Co-create plain-language RMP/REMS materials feedback loops; measure impact on behaviors (e.g., testing compliance, contraceptive adherence).
7. **Bridge drug–device vigilance:** Align PMS/PSUR requirements and create unified cross-product safety boards, especially where combination products are growing.
8. **Build LMIC capacity:** Expand VigiFlow onboarding, MedDRA training, and shared SOP "starter kits" to improve global signal coverage and comparability.

CONFLICT OF INTERESTS

The authors declare no conflict of interest

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AI TOOL DECLARATION

The authors declare that no AI and related tools are used to write the scientific content of this manuscript.

DATA AVAILABILITY

Data will be available on request

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